

WHAT IS CLAIMED IS:

1. Method for the production of recombinant DNA-derived tissue plasminogen activator (tPA), a tPA variant, a Kringle 2 Serine protease molecule (K2S) or a K2S variant in prokaryotic cells, wherein said tPA, tPA variant, K2S molecule or K2S variant is secreted extracellularly as an active and correctly folded protein, characterized in that the prokaryotic cell contains and expresses a vector comprising the DNA coding for said tPA, tPA variant, K2S molecule or K2S variant operably linked to the DNA coding for the signal peptide OmpA or a functional derivative thereof.

2. Method according to claim 1, characterised in that said the prokaryotic cell contains and expresses a vector comprising the DNA coding for said tPA, tPA variant, K2S molecule or K2S variant operably linked to the DNA coding for the signal peptide OmpA which is operably linked to the nucleic acid molecule defined by the sequence TCTGAGGGAAACAGTGAC (SEQ ID NO:1) or a functional derivative thereof.

3. Method according to claim 1 or 2, characterised in that the prokaryotic cell is *E. coli*.

4. Method according to one of claims 1 to 3, characterised in that the the following steps are carried out:

a) the DNA encoding the tPA, tPA variant, K2S molecule or K2S variant is amplified by PCR;

b) the PCR product is purified;

c) said PCR product is inserted into a vector comprising the DNA coding for OmpA signal peptide and the DNA coding for gpIII in such a way that said PCR product is operably linked upstream to the DNA coding for the OmpA signal sequence and linked downstream to the DNA coding for gpIII of said vector;

TCTGAGGGAAACAGTGAC

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- d) that a stop codon is inserted between said tPA, tPA variant, K2S molecule or K2S variant and gpIII;
- e) said vector is expressed by the prokaryotic cell;
- f) the tPA, tPA variant, K2S molecule or K2S variant is purified.

5. Method according to one of claims 1 to 4, characterised in that the vector is a phagemid vector comprising the DNA coding for OmpA signal peptide and the DNA coding for gpIII.

6. Method according to one of claims 1 to 5, characterised in that the vector is the pComb3HSS phagemid.

7. Method according to one of claims 1 to 6, characterised in that the DNA Sequence of OmpA linked upstream to K2S comprises the following sequence or a functional variant thereof or a variant due to the degenerate nucleotide code:

ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGTTTCG  
CTACCGTGGCCCAGGCGGCTCTGAGGGAAACAGTGACTGCTACTT  
TGGGAATGGGTCAGCCTACCGTGGCACGCACAGCCTCACCGAGTCG  
GGTGCCTCCTGCCTCCCGTGGGAATTCCATGATCCTGATAGGCAAGG  
TTTACACAGCACAGAACCCAGTGCCCAGGCACTGGGCCTGGGCA  
AACATAATTACTGCCGGAATCCTGATGGGGATGCCAAGCCCTGGTG  
CCACGTGCTGAAGAACCGCAGGCTGACGTGGGAGTACTGTGATGT  
GCCCTCCTGCTCCACCTGCGGCCTGAGACAGTACAGCCAGCCTCAG  
TTTCGCATCAAAGGAGGGCTCTTCGCCGACATCGCCTCCCACCCCT  
GGCAGGCTGCCATCTTTGCCAAGCACAGGAGGTCGCCCGGAGAGC  
GGTTCCTGTGCGGGGGCATACTCATCAGCTCCTGCTGGATTCTCTCT  
GCCGCCCACTGCTTCCAGGAGAGGTTTCCGCCCCACCACCTGACGG  
TGATCTTGGGCAGAACATAACCGGTGGTCCCTGGCGAGGAGGAGC  
AGAAATTTGAAGTCGAAAAATACATTGTCCATAAGGAATTCGATGA

Sub (a)  
TGACACTTACGACAATGACATTGCGCTGCTGCAGCTGAAATCGGAT  
TCGTCCCGCTGTGCCAGGAGAGCAGCGTGGTCCGCACTGTGTGCC  
TCCCCCGGCGGACCTGCAGCTGCCGGACTGGACGGAGTGTGAGCT  
CTCCGGCTACGGCAAGCATGAGGCCTTGTCTCCTTTCTATTTCGGAG  
CGGCTGAAGGAGGCTCATGTCAGACTGTACCCATCCAGCCGCTGCA  
CATCACAACATTTACTTAACAGAACAGTCACCGACAACATGCTGTG  
TGCTGGAGACACTCGGAGCGGCGGGCCCCAGGCAAACCTTGACGA  
CGCCTGCCAGGGCGATTTCGGGAGGCCCCCTGGTGTGTCTGAACGAT  
GGCCGCATGACTTTGGTGGGCATCATCAGCTGGGGCCTGGGCTGTG  
GACAGAAGGATGTCCCCGGGTGTGTACACAAAGGTTACCAACTACCT  
AGACTGGATTTCGTGACAACATGCGACCG (SEQ ID NO:2)

8. Method according to one of claims 1 to 7, characterised in that the DNA Sequence of OmpA comprises the following sequence:

ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGTTTCG  
CTACCGTGGCCCAGGCGGCC (SEQ ID NO:3)

9. Method according to one of claims 1 to 8, characterised in that the DNA Sequence of OmpA consists of the following sequence:

ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGTTTCG  
CTACCGTGGCCCAGGCGGCC (SEQ ID NO:3)

10. Method according to one of claims 1 to 9, characterised in that the DNA of the tPA, tPA variant, K2S molecule or K2S variant is preceded by a lac promotor and/or a ribosomal binding site.

11. Method according to one of claims 1 to 10, characterised in that the DNA coding for the tPA, tPA variant, K2S molecule or K2S variant is selected from the group of DNA molecules coding for at least 90% of the amino acids 87 – 527, 174 – 527, 180 – 527 or 220 – 527 of the human tissue plasminogen activator protein.

12. Method according to one of claims 5 to 11, characterised in that the DNA Sequence of K2S comprises the following sequence or a functional variant thereof or a variant due to the degenerate nucleotide code:

TCTGAGGGAAACAGTGACTGCTACTTTGGGAATGGGTCAGCCTACC  
GTGGCACGCACAGCCTCACCGAGTCGGGTGCCTCCTGCCTCCCGTG  
GAATTCCATGATCCTGATAGGCAAGGTTTACACAGCACAGAACCCC  
AGTGCCCAGGCACTGGGCCTGGGCAAACATAATTACTGCCGGAATC  
CTGATGGGGATGCCAAGCCCTGGTGCCACGTGCTGAAGAACCGCA  
GGCTGACGTGGGAGTACTGTGATGTGCCCTCCTGCTCCACCTGCGG  
CCTGAGACAGTACAGCCAGCCTCAGTTTCGCATCAAAGGAGGGCTC  
TTCGCCGACATCGCCTCCCACCCCTGGCAGGCTGCCATCTTTGCCA  
AGCACAGGAGGTCGCCCCGAGAGCGGTTCTGTGCGGGGGCATACT  
TCATCAGCTCCTGCTGGATTCTCTCTGCCGCCCCTGCTTCCAGGAG  
AGGTTTCCGCCCCACCACCTGACGGTGATCTTGGGCAGAACATACC  
GGGTGGTCCCTGGCGAGGAGGAGCAGAAATTTGAAGTCGAAAAAT  
ACATTGTCCATAAGGAATTCGATGATGACACTTACGACAATGACAT  
TGCGCTGCTGCAGCTGAAATCGGATTCGTCCCGCTGTGCCCAGGAG  
AGCAGCGTGGTCCGCACTGTGTGCCTTCCCCCGGCGGACCTGCAGC  
TGCCGGACTGGACGGAGTGTGAGCTCTCCGGCTACGGCAAGCATG  
AGGCCTTGTCTCCTTTCTATTTCGGAGCGGCTGAAGGAGGCTCATGT  
CAGACTGTACCCATCCAGCCGCTGCACATCACAACATTTACTTAAC  
AGAACAGTCACCGACAACATGCTGTGTGCTGGAGACACTCGGAGC  
GGCGGGCCCCAGGCAAACCTGCACGACGCCTGCCAGGGCGATTCTG  
GGAGGCCCCCTGGTGTGTCTGAACGATGGCCGCATGACTTTGGTGG  
GCATCATCAGCTGGGGCCTGGGCTGTGGACAGAAGGATGTCCCGG  
GTGTGTACACAAAGGTTACCAACTACCTAGACTGGATTTCGTGACAA  
CATGCGACCGTGA (SEQ ID NO:4).

13. Method according to one of claims 5 to 12, characterised in that the DNA Sequence of K2S consists of the following sequence:

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TCTGAGGGAAACACTGACTGCTACTTTGGGAATGGGTCAGCCTACC  
GTGGCACGCACAGCCTCACCGAGTCGGGTGCCTCCTGCCTCCCGTG  
GAATTCCATGATCCTGATAGGCAAGGTTTACACAGCACAGAACCCC  
AGTGCCCAGGCACTGGGCCTGGGCAAACATAATTACTGCCGGAATC  
CTGATGGGGATGCCAAGCCCTGGTGCCACGTGCTGAAGAACCGCA  
GGCTGACGTGGGAGTACTGTGATGTGCCCTCCTGCTCCACCTGCGG  
CCTGAGACAGTACAGCCAGCCTCAGTTTCGCATCAAAGGAGGGGCTC  
TTCGCCGACATCGCCTCCCACCCCTGGCAGGCTGCCATCTTTGCCA  
AGCACAGGAGGTCGCCCGGAGAGCGGTTCTGTGCGGGGGGCATAC  
TCATCAGCTCCTGCTGGATTCTCTCTGCCGCCCACTGCTTCCAGGAG  
AGGTTTCCGCCCCACCACCTGACGGTGATCTTGGGCAGAACATACC  
GGGTGGTCCCTGGCGAGGAGGAGCAGAAATTTGAAGTCGAAAAAT  
ACATTGTCCATAAGGAATTTCGATGATGACACTTACGACAATGACAT  
TGCGCTGCTGCAGCTGAAATCGGATTCGTCCCGCTGTGCCCAGGAG  
AGCAGCGTGGTCCGCACTGTGTGCCTTCCCCCGGCGGACCTGCAGC  
TGCCGGACTGGACGGAGTGTGAGCTCTCCGGCTACGGCAAGCATG  
AGGCCTTGTCTCCTTTCTATTTCGGAGCGGCTGAAGGAGGCTCATGT  
CAGACTGTACCCATCCAGCCGCTGCACATCACAACATTTACTTAAC  
AGAACAGTCACCGACAACATGCTGTGTGCTGGAGACACTCGGAGC  
GGCGGGCCCCAGGCAAACCTGCACGACGCCTGCCAGGGCGATTTCG  
GGAGGCCCCCTGGTGTGTCTGAACGATGGCCGCATGACTTTGGTGG  
GCATCATCAGCTGGGGCCTGGGCTGTGGACAGAAGGATGTCCCGG  
GTGTGTACACAAAGGTTACCAACTACCTAGACTGGATTTCGTGACAA  
CATGCGACCGTGA (SEQ ID NO:4).

14. DNA molecule characterized in that it is coding for:

a) the OmpA protein or a functional derivative thereof operably linked to

b) a DNA molecule coding for a polypeptide containing the kringle 2 domain and the serine protease domain of tissue plasminogen activator protein.

15. DNA molecule according to claim 14, characterized in that said DNA sequence comprises the following sequence or a functional variant thereof or a variant due to the degenerate nucleotide code:

ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGTTTCG  
CTACCGTGCGCCAGGCGGCCTCTGAGGGAAACAGTGACTGCTACTT  
TGGGAATGGGTCAGCCTACCGTGGCACGCACAGCCTCACCGAGTCG  
GGTGCCTCCTGCCTCCCGTGGAATTCCATGATCCTGATAGGCAAGG  
TTTACACAGCACAGAACCCCAAGTGCCCAGGCACTGGGCCTGGGCA  
AACATAATTACTGCCGGAATCCTGATGGGGATGCCAAGCCCTGGTG  
CCACGTGCTGAAGAACCGCAGGCTGACGTGGGAGTACTGTGATGT  
GCCCTCCTGCTCCACCTGCGGCCTGAGACAGTACAGCCAGCCTCAG  
TTTCGCATCAAAGGAGGGCTCTTCGCCGACATCGCCTCCCACCCCT  
GGCAGGCTGCCATCTTTGCCAAGCACAGGAGGTGCCCCGGAGAGC  
GGTTCCTGTGCGGGGGCATACTCATCAGCTCCTGCTGGATTCTCTCT  
GCCGCCCCTGCTTCCAGGAGAGGTTTCCGCCCCACCACCTGACGG  
TGATCTTGGGCAGAACATAACCGGTGGTCCCTGGCGAGGAGGAGC  
AGAAATTTGAAGTCGAAAAATACATTGTCCATAAGGAATTCGATGA  
TGACACTTACGACAATGACATTGCGCTGCTGCAGCTGAAATCGGAT  
TCGTCCCGCTGTGCCAGGAGAGCAGCGTGGTCCGCACTGTGTGCC  
TTCCCCCGGCGGACCTGCAGCTGCCGACTGGACGGAGTGTGAGCT  
CTCCGGCTACGGCAAGCATGAGGCCTTGTCTCCTTTCTATTTCGGAG  
CGGCTGAAGGAGGCTCATGTCAGACTGTACCCATCCAGCCGCTGCA  
CATCACAACATTTACTTAACAGAACAGTCACCGACAACATGCTGTG  
TGCTGGAGACACTCGGAGCGGCGGGCCCCAGGCAAACCTTGCACGA  
CGCCTGCCAGGGCGATTCTGGGAGGCCCCCTGGTGTGTCTGAACGAT  
GGCCGCATGACTTTGGTGGGCATCATCAGCTGGGGCCTGGGCTGTG  
GACAGAAGGATGTCCCGGGTGTGTACACAAAGGTTACCAACTACCT  
AGACTGGATTCTGTGACAACATGCGACCG (SEQ ID NO:5).

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SEQ ID NO: 5

16. DNA molecule according to claim 14 or 15, characterized in that said DNA sequence consists of the following sequence:

ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGTTTCG  
CTACCGTGGCCCAGGCGGCCTCTGAGGGAAACAGTGACTGCTACTT  
TGGGAATGGGTCAGCCTACCGTGGCACGCACAGCCTCACCGAGTCG  
GGTGCCTCCTGCCTCCCGTGGGAATTCCATGATCCTGATAGGCAAGG  
TTTACACAGCACAGAAACCCAGTGCCCAGGCACTGGGCCTGGGCA  
AACATAATTACTGCCGGAATCCTGATGGGGATGCCAAGCCCTGGTG  
CCACGTGCTGAAGAACCGCAGGCTGACGTGGGAGTACTGTGATGT  
GCCCTCCTGCTCCACCTGCGGCCTGAGACAGTACAGCCAGCCTCAG  
TTTCGCATCAAAGGAGGGCTCTTCGCCGACATCGCCTCCCACCCCT  
GGCAGGCTGCCATCTTTGCCAAGCACAGGAGGTGCCCCGGAGAGC  
GGTTCCTGTGCGGGGGCATACTCATCAGCTCCTGCTGGATTCTCTCT  
GCCGCCCACTGCTTCCAGGAGAGGTTTCCGCCCCACCACCTGACGG  
TGATCTTGGGCAGAACATAACCGGGTGGTCCCTGGCGAGGAGGAGC  
AGAAATTTGAAGTCGAAAAATACATTGTCCATAAGGAATTCGATGA  
TGACACTTACGACAATGACATTGCGCTGCTGCAGCTGAAATCGGAT  
TCGTCCCGCTGTGCCCAGGAGAGCAGCGTGGTCCGCACTGTGTGCC  
TTCCCCCGGCGGACCTGCAGCTGCCGGACTGGACGGAGTGTGAGCT  
CTCCGGCTACGGCAAGCATGAGGCCTTGTCTCCTTTCTATTTCGGAG  
CGGCTGAAGGAGGCTCATGTGAGACTGTACCCATCCAGCCGCTGCA  
CATCACAACATTTACTTAACAGAACAGTCACCGACAACATGCTGTG  
TGCTGGAGACACTCGGAGCGGCGGGCCCCAGGCAAACCTTGCACGA  
CGCCTGCCAGGGCGATTTCGGGAGGCCCCCTGGTGTGTCTGAACGAT  
GGCCGCATGACTTTGGTGGGCATCATCAGCTGGGGCCTGGGCTGTG  
GACAGAAGGATGTCCCGGGTGTGTACACAAAGGTTACCAACTACCT  
AGACTGGATTTCGTGACAACATGCGACCG (SEQ ID NO:5).

17. DNA molecule according to one of claims 14 to 16, characterized in that said DNA sequence b) is coding for at least 90% of the amino acids 87 – 527 of the human tissue plasminogen activator protein.

18. DNA molecule according to one of claims 14 to 17, characterized in that said DNA sequence b) is coding for at least 90% of the amino acids 174 – 527 of the human tissue plasminogen activator protein.

19. DNA molecule according to any one of claims 14 to 18, characterized in that said DNA sequence b) is coding for at least 90% of the amino acids 180 – 527 of the human tissue plasminogen activator protein.

20. DNA molecule according to any one of claims 14 to 19, characterized in that said DNA sequence b) is coding for at least 90% of the amino acids 220 – 527 of the human tissue plasminogen activator protein.

21. DNA molecule according to any one of claims 14 to 20, characterized in that said DNA sequence a) is hybridizing under stringent conditions to the following sequence:

ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGTTTCG  
CTACCGTGGCCCAGGCGGCC (SEQ ID NO:6).

22. DNA molecule according to any one of claims 14 to 21, characterized in that said DNA sequence a) consists of the following sequence:

ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGTTTCG  
CTACCGTGGCCCAGGCGGCC (SEQ ID NO:6).

23. DNA molecule according to any one of claims 14 to 22, characterized in that said DNA sequence b) is hybridizing under stringent conditions to the following sequence:

TCTGAGGGAAACAGTGACTGCTACTTTGGGAATGGGTCAGCCTACC  
GTGGCACGCACAGCCTCACCGAGTCGGGTGCCTCCTGCCTCCCGTG  
GAATTCCATGATCCTGATAGGCAAGGTTTACACAGCACAGAACCCC



AGTGCCCAAGGCACCTGGGCCTGGGCAAACATAATTACTGCCCGGAATC  
CTGATGGGGGATGCCAAGCCCTGGTGCCACGTGCTGAAGAACCGCA  
GGCTGACGTGGGAGTACTGTGATGTGCCCTCCTGCTCCACCTGCGG  
CCTGAGACAGTACAGCCAGCCTCAGTTTCGCATCAAAGGAGGGCTC  
TTCGCCGACATCGCCTCCCACCCCTGGCAGGCTGCCATCTTTGCCA  
AGCACAGGAGGTGCGCCCGGAGAGCGGTTCCCTGTGCGGGGGGCATAC  
TCATCAGCTCCTGCTGGATTCTCTCTGCCGCCCCTGCTTCCAGGAG  
AGGTTTCCGCCCCACCACCTGACGGTGATCTTGGGCAGAACATAACC  
GGGTGGTCCCTGGCGAGGAGGAGCAGAAATTTGAAGTCGAAAAAT  
ACATTGTCCATAAGGAATTCGATGATGACACTTACGACAATGACAT  
TGCCTGCTGCAGCTGAAATCGGATTCGTCCCGCTGTGCCCAGGAG  
AGCAGCGTGGTCCGCACTGTGTGCCTTCCCCCGGCGGACCTGCAGC  
TGCCGGACTGGACGGAGTGTGAGCTCTCCGGCTACGGCAAGCATG  
AGGCCTTGTCTCCTTTCTATTCGGAGCGGCTGAAGGAGGCTCATGT  
CAGACTGTACCCATCCAGCCGCTGCACATCACAACATTTACTTAAC  
AGAACAGTCACCGACAACATGCTGTGTGCTGGAGACACTCGGAGC  
GGCGGGCCCCAGGCAAACCTTGACGACGCCTGCCAGGGCGATTCTG  
GGAGGCCCCCTGGTGTGTCTGAACGATGGCCGCATGACTTTGGTGG  
GCATCATCAGCTGGGGCTGGGCTGTGGACAGAAGGATGTCCCGG  
GTGTGTACACAAAGGTTACCAACTACCTAGACTGGATTCTGTGACAA  
CATGCGACCGTGA (SEQ ID NO:7).

24. DNA molecule according to any one of claims 14 to 23, characterized in that said DNA sequence b) consists of the following sequence:

TCTGAGGGAAACAGTGACTGCTACTTTGGGAATGGGTCAGCCTACC  
GTGGCACGCACAGCCTCACCGAGTCGGGTGCCTCCTGCCTCCCGTG  
GAATTCCATGATCCTGATAGGCAAGGTTTACACAGCACAGAACCCC  
AGTGCCCAGGCACTGGGCCTGGGCAAACATAATTACTGCCGGAATC  
CTGATGGGGATGCCAAGCCCTGGTGCCACGTGCTGAAGAACCGCA  
GGCTGACGTGGGAGTACTGTGATGTGCCCTCCTGCTCCACCTGCGG

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CCTGAGACAGTACAGCCAGCCTCAGTTTCGCATCAAAGGAGGGCTC  
TTCGCCGACATCGCCTCCCACCCCTGGCAGGCTGCCATCTTTGCCA  
AGCACAGGAGGTGCCCCGAGAGCGGTTCTGTGCGGGGGGCATAC  
TCATCAGCTCCTGCTGGATTCTCTCTGCCGCCCACTGCTTCCAGGAG  
AGGTTTCCGCCCCACACCTGACGGTGATCTTGGGCAGAACATACC  
GGGTGGTCCCTGGCCAGGAGGAGCAGAAATTTGAAGTCGAAAAAT  
ACATTGTCCATAAGGAATTCGATGATGACACTTACGACAATGACAT  
TGCGCTGCTGCAGCTGAAATCGGATTCGTCCCGCTGTGCCCAGGAG  
AGCAGCGTGGTCCGCACTGTGTGCCTTCCCCCGGCGGACCTGCAGC  
TGCCGGACTGGACGGAGTGTGAGCTCTCCGGCTACGGCAAGCATG  
AGGCCTTGTCTCCTTTCTATTTCGGAGCGGCTGAAGGAGGCTCATGT  
CAGACTGTACCCATCCAGCCGCTGCACATCACAACATTTACTTAAC  
AGAACAGTCACCGACAACATGCTGTGTGCTGGAGACACTCGGAGC  
GGCGGGCCCCAGGCAAACCTGCACGACGCCTGCCAGGGGCGATTCTG  
GGAGGCCCCCTGGTGTGTCTGAACGATGGCCGCATGACTTTGGTGG  
GCATCATCAGCTGGGGCCTGGGCTGTGGACAGAAGGATGTCCCGG  
GTGTGTACACAAAGGTTACCAACTACCTAGACTGGATTCTGTGACAA  
CATGCGACCGTGA (SEQ ID NO:7).

25. Fusion protein of OmpA and K2S, characterised in that it comprises a protein characterized by the following amino acid sequence or a fragment, a functional variant, an allelic variant, a subunit, a chemical derivative or a glycosylation variant thereof:

MKKTAIAIAVALAGFATVAQAASEGNSDCYFGNGSAYRGTHSLTESG  
ASCLPWNSMILIGKVYTAQNPSAQALGLGKHNYCRNPDGDAKPWCH  
VLKNRRLTWEYCDVPSCSTCGLRQYSQPQFRIKGGLFADIASHPWQA  
AIFAKHRRSPGERFLCGGILISSCWILSAAHCFQERFPPHHLTIVLGRTY  
RVVPGEEEQKFEVEKYIVHKEFDDDTYDNDIALQLKSDSSRCAQESS  
VVRTVCLPPADLQLPDWTECELSGYGKHEALSPFYSERLKEAHVRLYP  
SSRCTSQHLLNRTVTDNMLCAGDTRSGGPQANLHDACQGDSGGPLVC

LNDGRMTLVGIISWGLGCGQKDVPGVYTKVTNYLDWIRDNM RPG  
(SEQ ID NO:8).

26. Fusion protein of OmpA and K2S according to claim 25, characterised in that it consists of a protein characterized by the following amino acid sequence:

MKKTAIAIAVALAGFATVAQAASEGNSDCYFGNGSAYRGTHSLTESG  
ASCLPWNSMILIGKVYTAQNPSAQALGLGKHNYCRNPDGDAKPWCH  
VLKNRRLTWEYCDVPSCSTCGLRQYSQPQFRIKGGLFADIASHPWQA  
AIFAKHRRSPGERFLCGGILISSCWILSAAHCFQERFPPHHLTIVILGR  
TYRVVPGEEEQKFEVEKYIVHKEFDDDDTYDNDIALQLKSDSSRCAQESS  
VVRTVCLPPADLQLPDWTECELSGYGKHEALSPFYSERLKEAHVRLYP  
SSRCTSQHLLNRTVTDNMLCAGDTRSGGPQANLHDACQGDSGGPLVC  
LNDGRMTLVGIISWGLGCGQKDVPGVYTKVTNYLDWIRDNM RPG  
(SEQ ID NO:8).

27. K2S protein, characterised in that it comprises a protein defined by the sequence SEGN (SEQ ID NO:9) and a or a variant or a fragment, a functional variant, an allelic variant, a subunit, a chemical derivative, a fusion protein or a glycosylation variant thereof.

28. K2S protein according to claim 27, characterised in that it comprises a protein defined by the sequence SEGNSD (SEQ ID NO:10) and a or a variant or a fragment, a functional variant, an allelic variant, a subunit, a chemical derivative, a fusion protein or a glycosylation variant thereof.

29. K2S protein according to claim 28 or 29, characterised in that it comprises a protein characterized by the following amino acid sequence or a fragment, a functional variant, an allelic variant, a subunit, a chemical derivative or a glycosylation variant thereof:

Sub 63  
SEGNSDCYFGNGSAYRGTHSLTESGASCLPWNSMILIGKVYTAQNPSA  
QALGLGKHNYCRNPDGDAKPWCHVLKNRRLTWEYCDVPSCSTCGLR  
QYSQPQFRIKGGLFADIASHPWQAAIFAKHRRSPGERFLCGGILISSCWI  
LSAAHCFQERFPPHLLTVILGR TYRVVPGE EEQKF EVEKYIVHKEFDD  
DTYDNDIAL LQLKSDSSRCAQESSVVRTVCLPPADLQLPDWTECELSG  
YGKHEALSPFYSERLKEAHVRLYPSSRCTSQHLLNRTVTDNMLCAGD  
TRSGGPQANLHDACQGD SGGPLVCLNDGRMTLVGIISWGLGCGQKD  
VPGVYTKVTNYLDWIRDNM RP\* (SEQ ID NO:11).

30. K2S according to any one of claims 27 to 30, characterised in that it consists of a protein characterized by the following amino acid sequence:

SEGNSDCYFGNGSAYRGTHSLTESGASCLPWNSMILIGKVYTAQNPSA  
QALGLGKHNYCRNPDGDAKPWCHVLKNRRLTWEYCDVPSCSTCGLR  
QYSQPQFRIKGGLFADIASHPWQAAIFAKHRRSPGERFLCGGILISSCWI  
LSAAHCFQERFPPHLLTVILGR TYRVVPGE EEQKF EVEKYIVHKEFDD  
DTYDNDIAL LQLKSDSSRCAQESSVVRTVCLPPADLQLPDWTECELSG  
YGKHEALSPFYSERLKEAHVRLYPSSRCTSQHLLNRTVTDNMLCAGD  
TRSGGPQANLHDACQGD SGGPLVCLNDGRMTLVGIISWGLGCGQKD  
VPGVYTKVTNYLDWIRDNM RP\* (SEQ ID NO:11).

31. A vector containing a DNA sequence according to any one of claims 14 to 24.

32. A vector according to claim 31, wherein said DNA sequence is preceeded by a lac promoter and a ribosomal binding site.

Sub 94  
33. The vector pComb3HSS containing a DNA according to any one of claims 14 to 24, wherein the expression of the gp III protein is suppressed or inhibited by deleting the DNA molecule encoding said gp III protein or by a stop codon between the gene coding for a a polypeptide

But a4  
containing the kringle 2 domain and the serine protease domain of tissue plasminogen activator protein and the protein III gene.

34. A prokaryotic host cell comprising a DNA molecule according to any one of claims 14 to 24.

35. A prokaryotic host cell comprising a vector according to any one of claims 31 to 33.

36. An *E. coli* host cell comprising a DNA molecule according to any one of claims 14 to 24.

37. An *E. coli* host cell comprising a vector according to any one of claims 31 to 33.

38. Use of a DNA molecule according to any one of claims 14 to 24 or of a vector according to any one of claims 31 to 33 or a host cell according to any one of claims 34 to 37 in a method for the production of a polypeptide having the activity of tissue plasminogen activator.

39. Use according to claim 38, wherein said method is a method according to any one of claims 1 to 13.